BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051506
Article Type:	Original research
Date Submitted by the Author:	22-Mar-2021
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Keywords:	Public health < INFECTIOUS DISEASES, COVID-19, Infection control < INFECTIOUS DISEASES

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Sex and gender differences in COVID-19: an Italian local register-based study

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Word count: 2778

Keywords: COVID-19; hospitalisation; virus clearance; death; sex differences; gender differences; Italy

ABSTRACT

Objectives

The present study aimed to explore differences in COVID-19 outcomes between male and female cases in the Apulian District of Foggia, Italy.

Design and setting

We performed a retrospective epidemiological study among COVID-19 confirmed cases occurred in the Apulian District of Foggia from February 29th to June 30th, 2020. The surveillance data from a regional registry (GIAVA-COVID©) were used.

Main outcomes

The main outcome measures were the proportion of hospitalisations, virus clearance and the case fatality rate.

Results

A total of 1,175 cases (50.7% female; median age: 55 years) were identified. The proportion of hospitalisation with COVID-19 diagnosis was 45.4% in men vs. 37.9% in women (p<0.01) while the average length of stay in hospitals was 31.3±14.6 days in women vs. 26.8±14.4 days in men (p<0.01). The proportion of cases who achieved virus clearance was higher in women (84.2%; days to clearance: 28.0±12.1) than in men (79.3%; days to clearance: 29.4±12.9; p<0.05). Men were associated with a significantly higher risk of dying from COVID-19 than women (case fatality rate [CFR] 16.1% vs. 10.4%; p<0.01). The mean time, from diagnosis to death was 14.5±14.4 days in women compared with 10.6±10.7 days in men (p<0.01). The male sex, age ≥55 years and underlying comorbidities significantly raised the risk of hospitalisation, persistent infection and death (p<0.05).

Conclusions

This study suggests that more attention should be paid to sex as a variable for the interpretation of COVID-19 data. Sex-disaggregated data will help the clinicians to make appropriate patient-tailored medical decisions.

Strengths and Limitations of this Study

- This study provides sex-disaggregated data of COVID-19 cases at a district level, in Italy. These data can contribute to a better understanding of who is being impacted the most by the pandemic and promote a patient-tailored treatment approach.
- The robust methodology of the present study enabled to accurately correlate the case demographics with COVID-19 clinical response. In this context, data related to the viral clearance, which reflect the diversified course of the disease according to the individual immune response, are confirmatory of sex difference in COVID-19.
- The data collected are highly homogeneous as they are strictly related to the first epidemic wave and provide an accurate picture of the impact of sex and age on COVID-19 outcomes in Italy during the initial phase of the pandemic.
- As the majority of the sex-disaggregated data available in the literature, the data presented in our study are not adjusted for lifestyle, profession, social or behavioural differences.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus causing the current pandemic, which has resulted in millions of infections and hundreds of thousands of deaths worldwide. As of March 10th 2021, a total of 3,069,625 cases of confirmed SARS-COV-2 have been reported in Italy with a case fatality rate (CFR) of 3.2%.[1]

The clinical manifestations of SARS-CoV-2 vary from asymptomatic infection to severe or critical disease.[2]

Older age and comorbidities such as hypertension, cardiovascular disease, diabetes, chronic respiratory disease are associated with severe disease and death.[3–5] Sex and gender have been identified as additional risk factors contributing to heterogeneous COVID-19 outcomes.[2] Indeed, several studies have reported sex bias in COVID-19 case fatalities. It is observed that men have a higher risk of developing a severe form of the disease compared with women, highlighting the importance of sex-disaggregated data of COVID-19 cases.[6] The initial reports from China followed by data from several European countries have shown similar numbers of confirmed cases between men and women.[7,8] However, the severity of COVID-19, measured as hospitalisation, admission to intensive care units and fatality rate, is 2-fold higher for men than women.[8,9] Studies in China, South Korea, United States, United Kingdom and Italy have reported higher case fatality rates and worst disease outcomes in male cases than in female cases.[7,10–14] In some of these studies, the higher fatality rate in men was observed even after adjusting for confounding factors such as age and comorbidities.[7,14] Additionally, in Italy, the higher fatality rate in men (age range: 40-80 years) is confirmed when the healthcare worker population is selectively studied.[1]

The reasons for the differences in COVID-19 outcome and progression between men and women remain unclear. On one hand, biological factors, such as chromosomal and hormonal differences between men and women, may influence their susceptibility to infections, immunologic responses and progression of the disease.[9,15–17] On the other hand, gender-related factors including psychological, social and behavioural differences between men and women may affect SARS-CoV-2 exposure, presence of comorbidities, treatment initiation and compliance, and COVID-19 mortality.[18,19]

In this study, we used the surveillance data from a regional registry containing all confirmed cases of COVID-19 occurred in the Foggia District (Apulia region, Italy), as of late June 2020, after the end

of the first epidemic wave. We aimed to explore the sex differences in hospitalisation, virus clearance, and deaths.

METHODS

Study population and design

We conducted a retrospective epidemiological study among COVID-19 cases occurred in the Foggia District, Apulia region, Italy, from February 29th to June 30th, 2020. Foggia District is the third-largest Apulian District, with an estimated 616,310 residents (51% women) as of January 1st 2020.[20]

We used the surveillance data from a regional registry (GIAVA – COVID©) developed based on the Go.Data outbreak investigation tool (WHO) to manage the emergency.[21] GIAVA – COVID© includes functionalities for investigation and follow-up of cases and contacts, contact tracing, laboratory and clinical data collection. Information collected include age, sex, residence location, date of illness onset, date of diagnosis, date of hospital admission, date of COVID-19 positive and negative tests, date of death, presence of underlying diseases, case outcomes (hospitalisation, virus clearance and death), and disease severity (mild, moderate, severe, or critical).[22] The disease classification is duly updated according to the change in clinical manifestations of each case.

This study included laboratory-confirmed cases defined as any person meeting the laboratory criterion (detection of SARS-CoV-2 nucleic acid or antigen in a clinical specimen).[23]

The proportion of hospitalisation was defined as the proportion of all infected individuals who were hospitalised among the total number of infected individuals. The proportion of individuals who achieved virus clearance was defined as the proportion of those clinically recovered and who had laboratory evidence of viral RNA clearance from the upper respiratory tract among the total number of infected individuals. The case fatality rate was defined as the proportion of deaths from diagnosed cases among the total number of infected individuals.

Statistical Analysis

Categorical variables were summarised as the counts and percentages in each category. Continuous variables were expressed as the medians and interquartile ranges (IQR) and the means (± standard deviation [SD]). Differences in continuous variables were tested with Student's t-test for normally distributed ones, or the Mann-Whitney U test when variables showed a non-normal distribution.

Significant differences in categorical variables were assessed using the Chi-square test or Fisher's exact test when appropriate. Multivariate logistic regression analysis was performed to evaluate whether demographics (sex: male vs. female; age group: above the median age vs. below the median age) and clinical characteristics were independently associated with hospitalisation, virus clearance, and deaths. The analysis was conducted with STATA/SE 15.0.

Patient and public involvement

Patients and/or the public were not involved either in the study design, conduct, reporting or in the dissemination plans of this research.

RESULTS

Between February 29th and June 30th, 2020, a total of 1,175 cases (50.7% female; median age: 55 years, IQR: 40-71 years) were diagnosed with COVID-19 in the Foggia District, Apulia region, Italy.

Comparison of demographics and clinical characteristics of men versus women are shown in Table 1. A total of 373 cases (31.7%) had underlying medical conditions, including cardiovascular disease (63.3%), diabetes (19.6%), chronic pulmonary disease (13.9%), cancer (10.7%), neurological diseases (9.9%), chronic kidney disease (9.4%), and obesity (with BMI between 30-40 kg/m^2 or higher) (6.7%). Nearly 50% of cases were asymptomatic or with mild disease, 14.4% had moderate disease, 20.9% developed a severe disease and 3.2% progressed to a critical stage. There was no significant difference in age, underlying comorbidities (with the exception of diabetes), and disease severity distributions between the male and female groups (Table 1).

Table 1. Comparison of characteristics between male and female COVID-19 cases in the Foggia District, Apulia region, Italy

Characteristics	Male	Female	Total	OR (95% CI)	$\chi 2$	p value
No. of cases (%)	579 (49.3)	596 (50.7)	1,175			
Median age (IQR), years	56 (40-70)	54.5 (38-74)	55 (40-71)			
Mean age (±SD), years	54.3±21.1	54.5±22.6	54.4±21.8			0.4291
Age group, No. (%):						
0-9	14 (2.4)	16 (2.7)	30 (2.6)	Ref.		
10-19	23 (4.0)	22 (3.7)	45 (3.8)	1.19 (0.43-3.34)	0.1	0.7061
20-29	43 (7.4)	53 (8.9)	96 (8.2)	0.93 (0.38-2.30)	0.03	0.8571
30-39	57 (9.8)	64 (10.7)	121 (10.3)	1.02 (0.42-2.47)	0.00	0.9655
40-49	91 (15.7)	95 (15.9)	186 (15.8)	1.09 (0.47-2.57)	0.05	0.8184
50-59	105 (18.1)	108 (18.1)	213 (18.1)	1.11 (0.48-2.59)	0.07	0.7874
60-69	96 (16.6)	64 (10.7)	160 (13.6)	1.71 (0.72-4.07)	1.84	0.1747
70-79	71 (12.3)	69 (11.6)	140 (11.9)	1.17 (0.49-2.81)	0.16	0.6874
80-89	64 (11.1)	72 (12.1)	136 (11.6)	1.01 (0.43-2.44)	0.00	0.9689
≥90	15 (2.6)	33 (5.5)	48 (4.1)	0.52 (0.18-1.48)	1.88	0.1705
Comorbidity, No (%)	191 (33.0)	182 (30.5)	373 (31.7)	1.1 (0.86-1.43)	0.75	0.3860
Cardiovascular disease	126 (66.9)	110 (60.4)	236 (63.3)	1.27 (0.81-1.97)	1.23	0.2682
Diabetes	49 (25.7)	24 (13.2)	73 (19.6)	2.27 (1.29-4.01)	9.20	0.0024
Chronic pulmonary disease	30 (15.7)	22 (12.1)	52 (13.9)	1.35 (0.72-2.58)	1.02	0.3132
Cancer	23 (12.0)	17 (9.3)	40 (10.7)	1.32 (0.65-2.75)	0.71	0.3994
Neurological diseases	15 (7.9)	22 (12.1)	37 (9.9)	0.62 (0.29-1.30)	1.87	0.1715
Chronic kidney disease	22 (11.5)	13 (7.1)	35 (9.4)	1.69 (0.78-3.78)	2.10	0.1475
Obesity	13 (6.8)	12 (6.6)	25 (6.7)	1.03 (0.42-2.55)	0.01	0.9345
Other metabolic diseases	5 (2.6)	10 (5.5)	15 (4.0)	0.46 (0.12-1.52)	2.00	0.1575
Liver disease	10 (5.2)	4 (2.2)	14 (3.8)	2.45 (0.69-10.91)	2.38	0.1228
Disease Severity, No. (%)						
Critical	23 (4.0)	15 (2.5)	38 (3.2)	1.88 (0.88-4.11)	3.15	0.0760
Severe	126 (21.8)	120 (20.1)	246 (20.9)	1.28 (0.87-1.90)	1.80	0.1796
Moderate	80 (13.8)	89 (14.9)	169 (14.4)	1.10 (0.72-1.69)	0.23	0.6348
Mild	165 (28.5)	197 (33.1)	362 (30.8)	1.02 (0.72-1.47)	0.03	0.8718
Asymptomatic	92 (15.9)	113 (19.0)	205 (17.4)	Ref.		

CI: confidence interval; IQR: interquartile range; OR: odds ratio; Ref.: reference group; SD: standard deviation

The proportion of hospitalisation with COVID-19 diagnosis was estimated to be 41.6%, with a significant difference observed between men (45.4%) and women (37.9%; p<0.01). While the average length of stay in hospitals was significantly higher in women (31.3±14.6 days) than in men (26.8±14.4 days; p<0.01), there were more women aged ≥55 years hospitalised (p<0.01). The proportion of cases who achieved virus clearance was 82%, higher in women (84.2%; days to clearance: 28.0±12.1) than in men (79.3%; days to clearance: 29.4±12.9; p<0.05). A total of 155 deaths occurred among all cases for an overall CFR of 13.2%. Men were associated with a significantly higher risk of dying from COVID-19 than women (16.1% vs. 10.4%; p<0.01). The mean time, from diagnosis to death was higher in women (14.5±14.4 days) compared with men (10.6±10.7 days; p<0.01) (Table 2).

Table 2. Comparison of outcomes between male and female COVID-19 cases in the Foggia District, Apulia region, Italy

Characteristics	Male	Female	OR (95% CI)	$\chi 2$	p value
Hospitalisation, No. (%)	263 (45.4)	226 (37.9)	1.36 (1.07-1.73)	6.81	0.0091
Mean age (± SD), years	66.2±16.0	70.2±18.8			0.0053
Mean length-of-stay in hospital (± SD), days	26.8±14.4	31.3±14.6			0.0032
Mean length-of-stay in hospital (IQR), days	24 (17-35)	29 (19-41)			
Virus clearance (yes), No. (%)	459 (79.3)	502 (84.2)	0.72 (0.53-0.97)	4.84	0.0278
Mean time-to-virus-clearance (± SD), days	29.4±12.9	28.0±12.1			0.0432
Median time-to-virus-clearance (IQR), days	25 (18-35)	27 (19-37)			
Deaths, No. (%)	93 (16.1)	62 (10.4)	1.65 (1.15-2.36)	8.21	0.0042
Mean time-to-death (± SD), days	10.6±10.7	14.5±14.4			0.0282
Median time-to-death (IQR), days	8 (3-16)	10 (4-23)			

CI: confidence interval; IQR: interquartile range; OR: odds ratio; SD: standard deviation

The male sex, age ≥55 years and underlying comorbidities significantly raised the risk of hospitalisation, persistent infection and death (p<0.05; Table 3).

Table 3. Multivariate logistic regression analysis of demographics and clinical characteristics of COVID-19 cases in the Foggia District, Apulia region, Italy

Characteristics	Hospitalisation		Virus clearance (no)		Deaths	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Sex (male vs. female)	1.52 (1.15-2.20)	0.003	1.51 (1.08-2.09)	0.014	2.33 (1.52-3.58)	0.000
Age group (≥55 years vs. <55 years)	1.83 (1.68-1.99)	0.000	1.62 (1.47-1.78)	0.000	2.62 (2.22-3.07)	0.000
Comorbidity (yes vs. no)	1.99 (1.47-2.69)	0.000	1.63 (1.16-2.29)	0.004	1.94 (1.28-2.93)	0.002

CI: confidence interval; OR: odds ratio

DISCUSSION

Our registry-based surveillance study of 1,175 COVID-19 cases, well characterised from both demographic and clinical points of view, highlighted a male bias in COVID-19 outcomes. Based on the herein presented data, men are more likely to be hospitalised compared with women and the proportion of male cases achieving virus clearance is lower compared with female cases. Furthermore, men require longer periods to achieve virus clearance, have a higher fatality rate and faster progression to death.

A male bias (male-to-female ratio >1.1) in COVID-19 mortality is currently reported in 75 of the 94 countries that have provided sex-disaggregated data (as of March 10th 2021). At the global level, a higher number of men are hospitalised or admitted to the intensive care unit (ICU) compared with women.[24] Additionally, several studies have demonstrated that men with COVID-19 are at higher risk of death and severe form of infection than women.[25,26] A recent meta-analysis of 3,111,714 reported global cases demonstrated that, whilst there is no difference in the proportion of male and female COVID-19 cases, men have higher odds of death (odds ratio [OR]=1.39; 95% confidence interval [CI]=1.31,1.47) compared with women.[27]. Similarly, our study presents a comparable proportion of women and men with confirmed COVID-19 (50.7% vs. 49.3%). Therefore, the observed differences cannot be attributed to a prevalence of COVID-19 in male sex.

The sex distribution of confirmed cases observed in the Foggia District, Apulia region is in line with the overall sex distribution of cases observed in Italy and other European countries.[1,8,28] Although in the early phase of the pandemic in Italy a higher prevalence of COVID-19 was observed in men compared with women, this disproportion became less evident with the progression of the

pandemic. This variability may be explained by the different surveillance approaches adopted during the pandemic since during the first epidemic wave a symptom-based screening led to an underestimation of asymptomatic to mild cases. In Italy, after the end of the first epidemic wave (June 30th 2020), a higher number of male cases was observed in the 0-9, 10-19, 60-69 and 70-79 years age groups (52.7%, 50.1%, 59.5%, 57.1%, respectively) compared with female cases, whereas a nearly 4-times higher number of female cases was observed in the >90 years age group.[29] On the contrary, as of March 10th 2021, the number of confirmed COVID-19 cases is slightly higher in women both in the overall Italian territory (51.4% in women vs. 48.6% in men) and in Apulia (51.% in women vs. 48.4% in men).[1,30]

Differences in disease incidence, morbidity and mortality between sexes have also been observed in other infectious diseases such as the severe acute respiratory syndrome coronavirus (SARS-COV-1) and the Middle East respiratory syndrome coronavirus (MERS-COV) with men being more susceptible than women to the infection and having worse outcome.[31,32] The difference in mortality between men and women suggests that women are either less prone to develop severe complications or that they are less likely to die because of severe complications.[33]

The reasons behind these sex-related differences are probably pathogen-specific and of multifactorial origin.[26] The three main determinants so far proposed to explain male-female disparities in SARS-CoV-2 infection are differences in immune function associated with the X chromosome, the effects of sex hormones, gender-related behavioural and socio-cultural differences.[2,6,16,17] For example, the localisation of angiotensin-converting enzyme-2 (ACE2) and Toll-like receptor 7 (TLR7) genes to the X chromosome and the mono-allelic versus the bi-allelic presence may help explain the increased risk of COVID-19 for males compared to females.[34]

From a biological point of view, women seem to have a stronger immune system, weaker cytokine-based pro-inflammatory response and lower levels of angiotensin-converting enzyme-2 (ACE2), an essential component for the entrance of COVID-19 into the cells.[2,16,35–37] In this context, oestrogens seem to play a key protective role. Oestrogen levels vary with age, rising in prepubertal individuals and decreasing with age. Thus, the age-associated decline in oestradiol levels might be an explanation for the higher susceptibility and severe progression of COVID-19 in older subjects.[38]

Our study highlights that, alongside sex, age and comorbidity are risk factors increasing hospitalisation and death, and decreasing virus clearance. That COVID-19 severity increases with

age became evident since the beginning of the pandemic. Early studies from China and Italy showed that older age was associated with a greater risk of developing acute respiratory distress syndrome (ARDS), severe lung disease and death.[5,10] A recent meta-analysis of 55 studies and 10,014 COVID-19 cases confirmed that older age (≥50 years), together with comorbidities, significantly affects the prognosis and severity of COVID-19.[3] A further study investigated whether male bias in COVID-19 mortality was maintained at every age. It analysed data collated by the National Institute for Demographic Studies from national statistical agencies across England and Wales, France, Germany, Italy, Netherlands, Portugal, Korea, and Spain, including a population of 194,349,591 men and 201,715,364 women from the beginning of the pandemic until June 21st 2020. The overall male-to-female mortality sex ratio per 100,000 population was 1.4 (crude ratio 1.3). This ratio varied with age: 0.81 for subjects aged 0-9 years; 1.9 in the 40-49 year age group, 2.3 in the 50-59 year age group; 2.6 in the 60-69 year age group and 1.65 in subjects older than 80 years.[39] How the male vs. female difference in mortality, hospitalisation and virus clearance progresses with age is an aspect that warrants further investigation. In this context, stratification of the sex-disaggregated data provided in our study by age group could be relevant to better understand to what extent women are genetically protected from COVID-19. Interestingly, in our study, the stratification of the population by a cut-off age of 55 years highlighted a higher hospitalisation rate in the subgroup of women aged ≥55 years, suggesting the role of the reduction of hormonal protection with age.

One of the main hypotheses that have been postulated to justify the observed sex heterogeneity in the immune response to SARS-CoV-2 infection is the different genetic profile. Increasing evidence from patient populations highlights a substantial contribution of human genetic factors to the diversified susceptibility to SARS-CoV-2 infection and/or COVID-19 severity. In this context, a differential response to COVID-19 has also been observed among individuals with ethnicity-based differences in their genetic profile.[34] For instance, the distribution of the gene cluster on chromosome 3, that has been recently identified as the major genetic risk factor for severe COVID-19, differs among populations of different ethnic background (i.e. Asian, European and African populations).[40]

Lastly, gender-related differences in lifestyles and social roles require careful considerations as they are believed to greatly influence the onset, course and outcome of COVID-19. It has been proposed that smoking and alcohol consumption, alongside poor eating habits, more frequently found in men than women, may lead to a higher incidence of comorbidities in men compared with women

explaining the higher male mortality observed on a global level.[18,41] However, it must be noted that no significant difference in underlying comorbidities (with the exception of diabetes) between men and women was found in our study. There may be other behavioural and social differences favouring women as men are more reluctant to follow hand hygiene and seek preventive care.[42] On the other hand, women might be more easily exposed to SARS-CoV-2 infection in both professional and household settings. Indeed, women represent 70% of the health and social care workforce and more often care for household members with COVID-19.[18,41]

The present study aimed to explore the differences in hospitalisation and death between men and women at the local level taking into consideration COVID-19 confirmed cases in the Apulian District of Foggia. The results are in line with what observed on a national and global level. Hospitalisation and death are hard outcomes for monitoring the course and severity of the disease. Furthermore, sex difference in virus clearance represents an added-value outcome of our study as it expresses the immune response of the host.

However, it should not be neglected that one of the main limitations of our study is that the presented data are not adjusted for lifestyle, profession, social or behavioural differences, all relevant factors that could change the interpretation of the data and could further emphasise the male-bias in COVID-19 severity and fatality. This limitation is a common feature of the majority of sex-disaggregated data currently available. Indeed, due to practicability and ethical reasons, no prospective study comparing an equal number of men and women under equal conditions of viral exposure has been conducted to date. Therefore, we highlight the need of taking into account the social, familiar and professional roles, alongside biological variables, in order to fully understand the differences in COVID-19 outcome between men and women.

The main strength of our study consists in its robust methodology, which enabled an accurate evaluation of the correlation between the case demographics (especially gender) and COVID-19 clinical response. Specifically, the collection of viral clearance data highlights a statistically significant male-to-female difference and provides a plausible explanation for the observed diversified course of the disease. Furthermore, the data collected in our study are highly homogeneous as they are strictly related to the first epidemic wave, and provide an accurate picture of the impact of sex and age on SARS-CoV-2 infection response in Italy during the initial phase of the pandemic. The ethnical composition of the population included in our study is also highly homogeneous and likely well representative of the Italian population or other Mediterranean European populations.

CONCLUSIONS

Despite a comparable incidence of COVID-19 among the two sexes, a male bias in COVID-19 mortality is observed in the majority of the countries with available sex-disaggregated data. Our study provides sex-disaggregated data for the COVID-19 cases of the Apulian district of Foggia, Italy. It demonstrates that male sex, alongside older age (age ≥55 years) and comorbidity, is associated with a greater risk of hospitalisation and death, and lower virus clearance. Therefore, more attention should be paid to sex as a variable for the interpretation of COVID-19 data. This study will help the clinicians to make appropriate patient-tailored medical decisions based on patient sex, age and comorbidities. Future investigations providing data adjusted for gender-related factors (social, familiar and professional roles) are warranted.

Acknowledgements The Authors would like to thank all the frontline health workers at Hospitals and Local Health Unit for their dedication and valuable work into pandemic control. A special thanks to Lucia Massi, Maria Rosa Valetto and Pietro Dri (Zadig, Scientific Publisher, Milan, Italy) for editorial assistance, manuscript development and writing support.

Contributors FF and RP conceptualised and designed the work, analysed and interpreted data, and wrote the manuscript. DM and PLL supervised the study, coordinated regional data collection and provided statistical support. SLC, TS and VD interpreted the results and critically reviewed the advanced version of the manuscript. All authors approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for profit sectors.

Competing interests The authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved either in the study design, conduct, reporting or in the dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval

The study was conducted in accordance with the principles expressed in the Declaration of Helsinki 1975, as revised in 2008. As this study constituted public health surveillance, ethical approval from institutional review board was not required. All data were provided and analysed anonymously.

Data availability statement No additional data available.

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STROBE Statement—checklist of items that should be included in reports of observational studies

Sex and gender differences in COVID-19: an Italian local register-based study
Francesca Fortunato, Domenico Martinelli, Sergio Lo Caputo, Teresa Santantonio, Vitangelo Dattoli, Pier Luigi Lopalco, and Rosa Prato.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 (title) 2 (abstract)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 (abstract)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 (lines 83-89)
Objectives	3	State specific objectives, including any prespecified hypotheses	5 (lines 92,93)
Methods			
Study design	4	Present key elements of study design early in the paper	5 (lines 97-99)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 (lines 100-107)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	*(a) Cross-sectional* 5 (lines 108,09)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 (lines 103-107)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 (lines 100,101; 110-115)
Bias	9	Describe any efforts to address potential sources of bias	5 (lines 144-147)
Study size	10	Explain how the study size was arrived at	5 (lines 97-99)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5 (lines 110-115)

Statistical methods		12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6 (lines 116-125)
			(*b*) Describe any methods used to examine subgroups and interactions	6 (lines 122-125)
			(*c*) Explain how missing data were addressed	Not applicable
			(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
			(*e*) Describe any sensitivity analyses	Not applicable
Results				
Participants		13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6 (lines 132,133) Table 1
			(b) Give reasons for non-participation at each stage	Not applicable
			(c) Consider use of a flow diagram	Not applicable
Descriptive data		14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6 (lines 132-140) Table 1
			(b) Indicate number of participants with missing data for each variable of interest	Not applicable
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data		15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
			Case-control study—Report numbers in each exposure category, or summary measures of exposure	
			Cross-sectional study—Report numbers of outcome events or summary measures	7-9 (lines 145-151) Tables 2,3
Main results		16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9 (lines 151-161) Tables 2,3
			(*b*) Report category boundaries when continuous variables were categorized	Tables 2,3
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses		17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9 (lines 160-161) Tables 2,3
Discussion				
Key results		18	Summarise key results with reference to study objectives	9 (lines 167-172)

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12 (lines 263-271)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12 (lines 283-281)
Generalisability	21	Discuss the generalisability (external validity) of the study results	12 (lines 272-281)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13 (lines 302,302)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Sex and gender differences in COVID-19: an Italian local register-based study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051506.R1
Article Type:	Original research
Date Submitted by the Author:	11-Jul-2021
Complete List of Authors:	Fortunato, Francesca; University of Foggia, Department of Medical and Surgical Sciences; Foggia University Hospital, Department of Hygiene Martinelli, Domenico; University of Foggia, Department of Medical and Surgical Sciences; Foggia University Hospital, Department of Hygiene Lo Caputo, Sergio; University of Foggia, Department of Clinical and Experimental Medicine; Foggia University Hospital, Infectious Diseases Unit Santantonio, Teresa; University of Foggia, Department of Clinical and Experimental Medicine; Foggia University Hospital, Infectious Diseases Unit Dattoli, Vitangelo; Foggia University Hospital Lopalco, Pier Luigi; University of Salento, Department of Biological and Environmental Sciences and Technology Prato, Rosa; University of Foggia, Department of Medical and Surgical Sciences; Foggia University Hospital, Department of Hygiene
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Infectious diseases
Keywords:	COVID-19, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, PUBLIC HEALTH, EPIDEMIOLOGY

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Sex and gender differences in COVID-19: an Italian local register-based study

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Word count: 2,853

Keywords: COVID-19; hospitalisation; virus clearance; death; sex differences; gender differences; Italy

ABSTRACT

Objectives

The present study aimed to explore differences in COVID-19 outcomes between male and female cases in the Apulian District of Foggia, Italy.

Design and setting

We performed a retrospective epidemiological study among all COVID-19 confirmed cases that occurred in the Apulian District of Foggia from February 29th to June 30th, 2020. The surveillance data from a regional registry (GIAVA-COVID©) were used.

Main outcomes

The main outcome measures were the proportion of hospitalisations, virus clearance and the case fatality rate.

Results

A total of 1,175 cases (50.7% female; median age: 55 years) were identified among 55,131 tests performed. The proportion of hospitalisation with COVID-19 diagnosis was 45.4% in men vs. 37.9% in women ($p<0.01$) while the average length of stay in hospitals was 31.3±14.6 days in women vs. 26.8±14.4 days in men ($p<0.01$). The proportion of cases who achieved virus clearance was higher in women (84.2%; days to clearance: 28.0±12.1) than in men (79.3%; days to clearance: 29.4±12.9; $p<0.05$). Men were associated with a significantly higher risk of dying from COVID-19 than women (case fatality rate [CFR] 16.1% vs. 10.4%; $p<0.01$). The mean time, from diagnosis to death was 14.5±14.4 days in women compared with 10.6±10.7 days in men ($p<0.01$). The male sex, age ≥55 years and presence of at least one underlying comorbidity significantly raised the risk of hospitalisation, persistent infection and death ($p<0.05$).

Conclusions

This study suggests that more attention should be paid to sex as a variable for the interpretation of COVID-19 data. Sex-disaggregated data will help clinicians to make appropriate patient-tailored medical decisions.

Strengths and Limitations of this Study

- This study provides sex-disaggregated data of COVID-19 cases at a district level, in Italy, contributing to a better understanding of who is being impacted the most by the pandemic and promoting a patient-tailored treatment approach.
- The robust methodology of the present study enabled to accurately correlate the case demographics with COVID-19 clinical response.
- The data related to the viral clearance, which reflect the diversified course of the disease according to the individual immune response, are confirmatory of sex difference in COVID-19.
- The data collected are highly homogeneous as they are strictly related to the first epidemic wave and provide an accurate picture of the impact of sex and age on COVID-19 outcomes in Italy during the initial phase of the pandemic.
- As the majority of the sex-disaggregated data available in the literature, the data presented in our study are not adjusted for lifestyle, profession, social or behavioural differences.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus causing the current pandemic, which has resulted in millions of infections and hundreds of thousands of deaths worldwide. As of March 10th 2021, a total of 3,069,625 cases of confirmed SARS-COV-2 have been reported in Italy with a case fatality rate (CFR) of 3.2%.[1]

The clinical manifestations of SARS-CoV-2 vary from asymptomatic infection to severe or critical disease.[2]

Older age and comorbidities such as hypertension, cardiovascular disease, diabetes, chronic respiratory disease are associated with severe disease and death.[3–5] Sex and gender have been identified as additional risk factors contributing to heterogeneous COVID-19 outcomes.[2] Indeed, several studies have reported sex bias in COVID-19 case fatalities. It is observed that men have a higher risk of developing a severe form of the disease compared with women, highlighting the importance of sex-disaggregated data of COVID-19 cases.[6] The initial reports from China followed by data from several European countries have shown similar numbers of confirmed cases between men and women.[7,8] However, the severity of COVID-19, measured as hospitalisation, admission to intensive care units (ICUs) and fatality rate, is 2-fold higher in men than women.[8,9] Studies in China, South Korea, United States, United Kingdom and Italy have reported higher case fatality rates and worst disease outcomes in male cases than in female cases.[7,10–14] In some of these studies, the higher fatality rate in men was observed even after adjusting for confounding factors such as age and comorbidities.[7,14] Additionally, in Italy, the higher fatality rate in men (age range: 40-80 years) is confirmed when the healthcare worker population is selectively studied.[1]

The reasons for the differences in COVID-19 outcome and progression between men and women remain unclear. On one hand, biological factors, such as chromosomal and hormonal differences between men and women, may influence their susceptibility to infections, immune responses and progression of the disease.[9,15–17] On the other hand, gender-related factors including psychological, social and behavioural differences between men and women may affect SARS-CoV-2 exposure, presence of comorbidities, treatment initiation and compliance, and COVID-19 mortality.[18,19]

In this study, we used the surveillance data from a regional registry containing all confirmed cases of COVID-19 that occurred in the Foggia District (Apulia region, Italy), as of late June 2020, after the

end of the first epidemic wave. We aimed to explore the sex differences in hospitalisation, virus clearance, and deaths.

METHODS

Study population and design

We conducted a retrospective epidemiological study among COVID-19 cases that occurred in the Foggia District, Apulia region, Italy, from February 29th to June 30th, 2020. Foggia District is the third-largest Apulian District, with an estimated population of 616,310 residents (51% women) as of January 1st 2020.[20]

We used the surveillance data from a regional registry (GIAVA – COVID©) which was developed based on the WHO Go.Data outbreak investigation tool to manage the emergency.[21] GIAVA – COVID© includes functionalities for investigation and follow-up of cases and contacts, contact tracing, laboratory and clinical data collection. The collected information includes age, sex, residence location, date of disease onset, date of diagnosis, date of hospital admission, date of COVID-19 test results (positive or negative), date of death, presence of underlying diseases, case outcomes (hospitalisation, virus clearance and death), and disease severity (mild, moderate, severe, or critical).[22] The disease classification was duly updated according to clinical evolution of each case.

This study included all laboratory-confirmed cases defined as any person meeting the laboratory criterion (i.e. detection of SARS-CoV-2 nucleic acid or antigen in a clinical specimen).[23]

The proportion of hospitalisation was defined as the proportion of infected individuals undergoing hospitalisation among the total number of infected individuals. The proportion of individuals who achieved virus clearance was defined as the proportion of clinically recovered individuals with laboratory evidence of viral RNA clearance from the upper respiratory tract (two serial negative PCR tests at least 24 hours apart) among the total number of infected individuals. The case fatality rate was defined as the proportion of deaths among the total number of confirmed cases.

Statistical Analysis

Categorical variables were summarised as counts and percentages in each category. Data for continuous variables were expressed as medians (interquartile ranges [IQR]) and means (± standard

deviation [SD]). Normality of data was tested by the Kolmogorov-Smirnov test. Differences in continuous variables were assessed with Student's t-test or Mann-Whitney U test, depending on whether continuous variables were normally distributed or not, respectively. Significant differences in categorical variables were assessed using the Chi-square test or Fisher's exact test when appropriate and the odds ratio (OR) with 95% confidence interval (CI). Multivariate logistic regression analysis was performed to evaluate whether demographics (sex: male vs. female; age group: above vs. below the median age) and clinical characteristics (presence vs. absence of at least one underlying medical condition) were independently associated with hospitalisation, virus clearance, and deaths. The analysis was conducted with STATA/SE 15.0.

RESULTS

Between February 29th and June 30th, 2020, a total of 1,175 cases (50.7% female; median age: 55 years, IQR: 40-71 years) were diagnosed with COVID-19 in the Foggia District, Apulia region, Italy. The female positivity rate was 2.02% among 29,475 tests performed and the male positivity rate was 2.25% among 25,656 tests performed (chi-square p >0.05).

Comparison of demographics and clinical characteristics of men versus women are shown in Table 1. A total of 373 cases (31.7%) had underlying medical conditions, including cardiovascular disease (63.3%), diabetes (19.6%), chronic pulmonary disease (13.9%), cancer (10.7%), neurological diseases (9.9%), chronic kidney disease (9.4%), and obesity (with body mass index [BMI] between 30-40 kg/m^2 or higher) (6.7%). Nearly 50% of cases were asymptomatic or with mild disease, 14.4% had moderate disease, 20.9% developed a severe disease and 3.2% progressed to a critical stage. There was no significant difference in age, underlying comorbidities (with the exception of diabetes), and disease severity distributions between the male and female groups (Table 1).

Table 1. Comparison of characteristics between male and female COVID-19 cases in the Foggia District, Apulia region, Italy

Characteristics	Male	Female	Total	OR (95% CI)	$\chi 2$	p value
No. of cases (%)	579 (49.3)	596 (50.7)	1,175			
Median age (IQR), years	56 (40-70)	54.5 (38-74)	55 (40-71)			
Mean age (±SD), years	54.3±21.1	54.5±22.6	54.4±21.8			0.4291
Age group, No. (%):						
0-9	14 (2.4)	16 (2.7)	30 (2.6)	Ref.		
10-19	23 (4.0)	22 (3.7)	45 (3.8)	1.19 (0.43-3.34)	0.1	0.7061
20-29	43 (7.4)	53 (8.9)	96 (8.2)	0.93 (0.38-2.30)	0.03	0.8571
30-39	57 (9.8)	64 (10.7)	121 (10.3)	1.02 (0.42-2.47)	0.00	0.9655
40-49	91 (15.7)	95 (15.9)	186 (15.8)	1.09 (0.47-2.57)	0.05	0.8184
50-59	105 (18.1)	108 (18.1)	213 (18.1)	1.11 (0.48-2.59)	0.07	0.7874
60-69	96 (16.6)	64 (10.7)	160 (13.6)	1.71 (0.72-4.07)	1.84	0.1747
70-79	71 (12.3)	69 (11.6)	140 (11.9)	1.17 (0.49-2.81)	0.16	0.6874
80-89	64 (11.1)	72 (12.1)	136 (11.6)	1.01 (0.43-2.44)	0.00	0.9689
≥90	15 (2.6)	33 (5.5)	48 (4.1)	0.52 (0.18-1.48)	1.88	0.1705
Comorbidity, No (%)						
None	388 (67.0)	414 (69.5)	802 (68.3)	Ref.		
At least one comorbidity	191 (33.0)	182 (30.5)	373 (31.7)	1.1 (0.86-1.43)	0.75	0.3860
Cardiovascular disease	126 (66.9)	110 (60.4)	236 (63.3)	1.27 (0.81-1.97)	1.23	0.2682
Diabetes	49 (25.7)	24 (13.2)	73 (19.6)	2.27 (1.29-4.01)	9.20	0.0024
Chronic pulmonary disease	30 (15.7)	22 (12.1)	52 (13.9)	1.35 (0.72-2.58)	1.02	0.3132
Cancer	23 (12.0)	17 (9.3)	40 (10.7)	1.32 (0.65-2.75)	0.71	0.3994
Neurological diseases	15 (7.9)	22 (12.1)	37 (9.9)	0.62 (0.29-1.30)	1.87	0.1715
Chronic kidney disease	22 (11.5)	13 (7.1)	35 (9.4)	1.69 (0.78-3.78)	2.10	0.1475
Obesity	13 (6.8)	12 (6.6)	25 (6.7)	1.03 (0.42-2.55)	0.01	0.9345
Other metabolic diseases	5 (2.6)	10 (5.5)	15 (4.0)	0.46 (0.12-1.52)	2.00	0.1575
Liver disease	10 (5.2)	4 (2.2)	14 (3.8)	2.45 (0.69-10.91)	2.38	0.1228
Disease Severity, No. (%)						
Asymptomatic	92 (15.9)	113 (19.0)	205 (17.4)	Ref.		
Critical	23 (4.0)	15 (2.5)	38 (3.2)	1.88 (0.88-4.11)	3.15	0.0760
Severe	126 (21.8)	120 (20.1)	246 (20.9)	1.28 (0.87-1.90)	1.80	0.1796
Moderate	80 (13.8)	89 (14.9)	169 (14.4)	1.10 (0.72-1.69)	0.23	0.6348
Mild	165 (28.5)	197 (33.1)	362 (30.8)	1.02 (0.72-1.47)	0.03	0.8718

CI: confidence interval; IQR: interquartile range; OR: odds ratio; Ref.: reference group; SD: standard deviation

The proportion of hospitalisation among COVID-19 cases was estimated to be 41.6%, with a significant difference observed between men (45.4%) and women (37.9%; p<0.01). While the average length of stay in hospitals was significantly higher in women (31.3±14.6 days) than in men (26.8±14.4 days; p<0.01), there were more women aged ≥55 years hospitalised (p<0.01). The proportion of cases who achieved virus clearance was 82%, higher in women (84.2%; days to clearance: 28.0±12.1) than in men (79.3%; days to clearance: 29.4±12.9; p<0.05). A total of 155 deaths occurred among all cases for an overall CFR of 13.2%. Men were associated with a significantly higher risk of dying from COVID-19 than women (16.1% vs. 10.4%; p<0.01). The mean time, from diagnosis to death was higher in women (14.5±14.4 days) compared with men (10.6±10.7 days; p<0.01) (Table 2).

Table 2. Comparison of outcomes between male and female COVID-19 cases in the Foggia District, Apulia region, Italy

Characteristics	Male	Female	OR (95% CI)	$\chi 2$	p value
Hospitalisation, No. (%)	263 (45.4)	226 (37.9)	1.36 (1.07-1.73)	6.81	0.0091
Mean age (± SD), years	66.2±16.0	70.2±18.8			0.0053
Mean length-of-stay in hospital (± SD), days	26.8±14.4	31.3±14.6			0.0032
Median length-of-stay in hospital (IQR), days	24 (17-35)	29 (19-41)			
Virus clearance (yes), No. (%)	459 (79.3)	502 (84.2)	0.72 (0.53-0.97)	4.84	0.0278
Mean time-to-virus-clearance (± SD), days	29.4±12.9	28.0±12.1			0.0432
Median time-to-virus-clearance (IQR), days	25 (18-35)	27 (19-37)			
Deaths, No. (%)	93 (16.1)	62 (10.4)	1.65 (1.15-2.36)	8.21	0.0042
Mean time-to-death (± SD), days	10.6±10.7	14.5±14.4			0.0282
Median time-to-death (IQR), days	8 (3-16)	10 (4-23)			

CI: confidence interval; IQR: interquartile range; OR: odds ratio; SD: standard deviation

The male sex, age ≥55 years and underlying comorbidities (presence of at least a condition among those listed in Table 1) significantly raised the risk of hospitalisation, persistent infection and death (p<0.05; Table 3).

Table 3. Multivariate logistic regression analysis of demographics and clinical characteristics of COVID-19 cases in the Foggia District, Apulia region, Italy

Characteristics	Hospitalisation		Virus clearance (no)		Deaths	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Sex (male vs. female)	1.52 (1.15-2.20)	0.003	1.51 (1.08-2.09)	0.014	2.33 (1.52-3.58)	0.000
Age group (≥55 years vs. <55 years)	1.83 (1.68-1.99)	0.000	1.62 (1.47-1.78)	0.000	2.62 (2.22-3.07)	0.000
At least one comorbidity (yes vs. no)	1.99 (1.47-2.69)	0.000	1.63 (1.16-2.29)	0.004	1.94 (1.28-2.93)	0.002

CI: confidence interval; OR: odds ratio

DISCUSSION

Our registry-based surveillance study of 1,175 COVID-19 cases, well characterised from both demographic and clinical points of view, highlighted a male bias in COVID-19 outcomes. Based on the herein presented data, men are more likely to be hospitalised than women and the proportion of male cases achieving virus clearance is lower compared with female cases. Furthermore, men require longer periods to achieve virus clearance, have a higher fatality rate and faster progression to death.

A male bias (male-to-female ratio >1.1) in COVID-19 mortality is currently reported in 75 of the 94 countries that have provided sex-disaggregated data (as of March 10th 2021). At the global level, a higher number of men are hospitalised or admitted to ICU compared with women.[24] Additionally, several studies have demonstrated that men with COVID-19 are at higher risk of death and severe form of infection than women.[25,26] A recent meta-analysis of 3,111,714 reported global cases demonstrated that, whilst there is no difference in the proportion of male and female COVID-19 cases, men have higher odds of death (OR=1.39; 95% CI=1.31,1.47) compared with women.[27]. Similarly, our study presents a comparable proportion of women and men with confirmed COVID-19 (50.7% vs. 49.3%) and similar rates of positivity for infection (2.02% vs. 2.25%, p >0.05). Therefore, the observed differences cannot be attributed to a prevalence of COVID-19 in the male sex.

The sex distribution of confirmed cases observed in the Foggia District, Apulia region is in line with the overall sex distribution of cases observed in Italy and other European countries.[1,8,28] Although in the early phase of the pandemic in Italy a higher prevalence of COVID-19 was observed

in men compared with women, this disproportion became less evident with the progression of the pandemic. This variability may be explained by the different surveillance approaches adopted during the pandemic since a symptom-based screening led to an underestimation of asymptomatic to mild cases during the first epidemic wave. In Italy, after the end of the first epidemic wave (June 30th 2020), a higher number of male cases was observed in the 0-9, 10-19, 60-69 and 70-79 years age groups (52.7%, 50.1%, 59.5%, 57.1%, respectively) compared with female cases, whereas a nearly 4-times higher number of female cases was observed in the >90 years age group.[29] On the contrary, as of March 10th 2021, the number of confirmed COVID-19 cases is slightly higher in women both in the overall Italian territory (51.4% in women vs. 48.6% in men) and in Apulia (51.% in women vs. 48.4% in men).[1,30]

Differences in disease incidence, morbidity and mortality between sexes have also been observed in other infectious diseases such as the severe acute respiratory syndrome coronavirus (SARS-COV-1) and the Middle East respiratory syndrome coronavirus (MERS-COV) with men being more susceptible than women to the infection and having a worse outcome.[31,32] The difference in mortality between men and women suggests that women are either less prone to develop severe complications or are less likely to die because of severe complications.[33]

The reasons behind these sex-related differences are probably pathogen-specific and of multifactorial origin.[26] The three main determinants so far proposed to explain male-female disparities in SARS-CoV-2 infection are differences in immune function associated with the X chromosome, the effects of sex hormones, gender-related behavioural and socio-cultural differences.[2,6,16,17] For example, the localisation of angiotensin-converting enzyme-2 (ACE2) and Toll-like receptor 7 (TLR7) genes in the X chromosome and the mono-allelic versus the bi-allelic presence may help explain the increased risk of COVID-19 for males compared with females.[34]

From a biological point of view, women seem to have a stronger immune system, weaker cytokine-based pro-inflammatory response and lower levels of ACE2, an essential component for the entrance of COVID-19 into the cells.[2,16,35–37] In this context, oestrogens seem to play a key protective role. Oestrogen levels vary with age, rising in prepubertal individuals and decreasing with age. Thus, the age-associated decline in oestradiol levels might be an explanation for the higher susceptibility and severe progression of COVID-19 in older subjects.[38]

Our study highlights that, alongside sex, age and comorbidity are risk factors increasing hospitalisation and death, and decreasing virus clearance. That COVID-19 severity increases with

age became evident since the beginning of the pandemic. Early studies from China and Italy showed that older age was associated with a greater risk of developing acute respiratory distress syndrome (ARDS), severe lung disease and death.[5,10] A recent meta-analysis of 55 studies and 10,014 COVID-19 cases confirmed that older age (≥50 years), together with comorbidities, significantly affects the prognosis and severity of COVID-19.[3] A further study investigated whether male bias in COVID-19 mortality was maintained at every age. It analysed data collated by the National Institute for Demographic Studies from national statistical agencies across England and Wales, France, Germany, Italy, Netherlands, Portugal, Korea, and Spain, including a population of 194,349,591 men and 201,715,364 women from the beginning of the pandemic until June 21st 2020. The overall male-to-female mortality sex ratio per 100,000 population was 1.4 (crude ratio 1.3). This ratio varied with age: 0.81 for subjects aged 0-9 years; 1.9 in the 40-49 year age group, 2.3 in the 50-59 year age group; 2.6 in the 60-69 year age group and 1.65 in subjects older than 80 years.[39] How the male vs. female difference in mortality, hospitalisation and virus clearance progresses with age is an aspect that warrants further investigation. In this context, stratification of the sex-disaggregated data provided in our study by age group could be relevant to better understand to what extent women are genetically protected from COVID-19. Interestingly, in our study, the stratification of the population by a cut-off age of 55 years highlighted a higher hospitalisation rate in the subgroup of women aged ≥55 years, suggesting the role of the reduction of hormonal protection with age.

One of the main hypotheses that have been postulated to justify the observed sex heterogeneity in the immune response to SARS-CoV-2 infection is the different genetic profile. Increasing evidence from patient populations highlights a substantial contribution of human genetic factors to the diversified susceptibility to SARS-CoV-2 infection and/or COVID-19 severity. In this context, a differential response to COVID-19 has also been observed among individuals with ethnicity-based differences in their genetic profile.[34] For instance, the distribution of the gene cluster on chromosome 3, that has been recently identified as the major genetic risk factor for severe COVID-19, differs among populations of different ethnic background (i.e. Asian, European and African populations).[40]

Lastly, gender-related differences in lifestyles and social roles require careful considerations as they are believed to greatly influence the onset, course and outcome of COVID-19. It has been proposed that smoking and alcohol consumption, alongside poor eating habits, more frequently found in men than women, may lead to a higher incidence of comorbidities in men compared with women

explaining the higher male mortality observed on a global level.[18,41] However, it must be noted that no significant difference in underlying comorbidities (except for diabetes) between men and women was found in our study. There may be other behavioural and social differences favouring women as men are more reluctant to follow hand hygiene and seek preventive care.[42] On the other hand, women might be more easily exposed to SARS-CoV-2 infection in both professional and household settings. Indeed, women represent 70% of the health and social care workforce and more often care for household members with COVID-19.[18,41]

The present study aimed to explore the differences in hospitalisation and death between men and women at the local level taking into consideration COVID-19 confirmed cases in the Apulian District of Foggia. The results are in line with what observed on a national and global level. Hospitalisation and death are hard outcomes for monitoring the course and severity of the disease. Furthermore, sex difference in virus clearance represents an added-value outcome of our study as it expresses the immune response of the host.

However, it should not be neglected that one of the main limitations of our study is that the presented data are not adjusted for lifestyle, profession, social or behavioural differences, all relevant factors that could change the interpretation of the data and could further emphasise the male-bias in COVID-19 severity and fatality. This limitation is a common feature of the majority of sex-disaggregated data currently available. Indeed, due to practicability and ethical reasons, no prospective study comparing an equal number of men and women under equal conditions of viral exposure has been conducted to date. Therefore, we highlight the need of taking into account the social, familiar and professional roles, alongside biological variables, in order to fully understand the differences in COVID-19 outcome between men and women.

The main strength of our study consists in its robust methodology, which enabled an accurate evaluation of the correlation between the case demographics (especially gender) and COVID-19 clinical response. Specifically, the collection of viral clearance data highlights a statistically significant male-to-female difference and provides a plausible explanation for the observed diversified course of the disease. Furthermore, the data collected in our study are highly homogeneous as they are strictly related to the first epidemic wave, and provide an accurate picture of the impact of sex and age on SARS-CoV-2 infection response in Italy during the initial phase of the pandemic. The ethnic composition of the population included in our study is also highly homogeneous and likely well representative of the Italian population or other Mediterranean European populations.

CONCLUSIONS

Despite a comparable incidence of COVID-19 among the two sexes, a male bias in COVID-19 mortality is observed in the majority of the countries with available sex-disaggregated data. Our study provides sex-disaggregated data for the COVID-19 cases of the Apulian district of Foggia, Italy. It demonstrates that male sex, alongside older age (age ≥55 years) and presence of at least one comorbidity, is associated with a greater risk of hospitalisation and death, and lower virus clearance. Therefore, more attention should be paid to sex as a variable for the interpretation of COVID-19 data. This study will help clinicians to make appropriate patient-tailored medical decisions based on patient sex, age and comorbidities. Future investigations providing data adjusted for gender-related factors (social, familiar and professional roles) are warranted.

Acknowledgements The Authors would like to thank all the frontline health workers at Hospitals and Local Health Unit for their dedication and valuable work into pandemic control. A special thanks to Lucia Massi, Maria Rosa Valetto and Pietro Dri (Zadig, Scientific Publisher, Milan, Italy) for editorial assistance, manuscript development and writing support.

Contributors FF and RP conceptualised and designed the work, analysed and interpreted data, and wrote the manuscript. DM and PLL supervised the study, coordinated regional data collection and provided statistical support. SLC, TS and VD interpreted the results and critically reviewed the advanced version of the manuscript. All authors approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for profit sectors.

Competing interests The authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved either in the study design, conduct, reporting or in the dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval

The study was conducted in accordance with the principles expressed in the Declaration of Helsinki 1975, as revised in 2008. As this study constituted public health surveillance, ethical approval from institutional review board was not required. All data were provided and analysed anonymously.

Data availability statement No additional data available.

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STROBE Statement—checklist of items that should be included in reports of observational studies

Sex and gender differences in COVID-19: an Italian local register-based study
Francesca Fortunato, Domenico Martinelli, Sergio Lo Caputo, Teresa Santantonio, Vitangelo Dattoli, Pier Luigi Lopalco, and Rosa Prato.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 (title) 2 (abstract)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 (abstract)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 (lines 65-92)
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5 (lines 92,96)
Methods			
Study design	4	Present key elements of study design early in the paper	5 (lines 100-103)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 (lines 100-112)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	*(a) Cross-sectional* 5 (lines 115-120)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 (lines 103-107)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 (lines 104-107; 115-132)
Bias	9	Describe any efforts to address potential sources of bias	5-6 (lines 128-132)
Study size	10	Explain how the study size was arrived at	5-6 (lines 113-114)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6 (lines 121-132)

Statistical methods		12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6 (lines 121-132)
			(*b*) Describe any methods used to examine subgroups and interactions	5-6 (lines 121-132)
			(*c*) Explain how missing data were addressed	Not applicable
			(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
			(*e*) Describe any sensitivity analyses	Not applicable
Results				
Participants		13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6 (lines 138-149) Table 1
			(b) Give reasons for non-participation at each stage	Not applicable
			(c) Consider use of a flow diagram	Not applicable
Descriptive data		14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7 (lines 132-140) Table 1
			(b) Indicate number of participants with missing data for each variable of interest	Not applicable
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data		15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
			Case-control study—Report numbers in each exposure category, or summary measures of exposure	
			Cross-sectional study—Report numbers of outcome events or summary measures	8-9 (lines 154-175) Tables 2, 3
Main results		16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9 (lines 154-175) Tables 2, 3
			(*b*) Report category boundaries when continuous variables were categorized	Tables 2,3
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses		17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 2,3
Discussion				
Key results		18	Summarise key results with reference to study objectives	9 (lines 177-182)

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12 (lines 273-281)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12 (lines 282-291)
Generalisability	21	Discuss the generalisability (external validity) of the study results	13 (lines 292-301)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13 (lines 312,313)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.